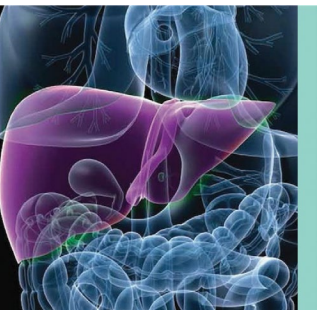

Pharmacological, Endoscopic, Metabolic, and Surgical Procedures for Nonalcoholic Fatty Liver Disease

Stavra A. Xanthakos, M.D., M.S.

For patients with nonalcoholic fatty liver disease (NAFLD), first-line treatment remains lifestyle interventions to improve diet and activity and to reduce excess adiposity. Losing weight correlates with histological improvement in both children and adults with NAFLD.[1,2] However, many patients face challenges in implementing and maintaining the required lifestyle changes. In most studies, less than half achieve resolution of nonalcoholic steatohepatitis (NASH), and even fewer resolve NAFLD completely.[1,2] When lifestyle interventions alone are insufficient, adjunctive treatment may include pharmacological or metabolic bariatric procedures, particularly in patients with progressive fibrosis.

At present, no regulatory agency has approved pharmacotherapy specifically for treatment of NAFLD or NASH. Based on supportive clinical trials, American Association for the Study of Liver Diseases clinical practice guidelines have recommended off-label pioglitazone to treat NASH in adults with or without diabetes, or high-dose vitamin E (800 IU/day) for adults with NASH without diabetes.[3] Over the last decade, expanded understanding of the complex pathophysiology of

Abbreviations: ACC, acetyl coenzymes A carboxylase; ASBT, apical sodium-dependent bile acid transporter; ASK1, apoptosis signal-regulating kinase 1; CB1, cannabinoid receptor 1; CCR, C-C motif chemokine receptor; CI, confidence interval; CPAP, continuous positive airway pressure; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FAS, fatty acid synthetase; FDA, US Food and Drug Administration; FGF, fibroblast growth factor; FMT, fecal microbiota transplant; FXR, farnesoid X receptor; GLP1, glucagon-like peptide 1; LXR, liver X receptor; mTOT, mitochondrial target of thiazolidinediones; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; RYGB, Roux-en-Y gastric bypass; SGLT 2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; TGR5, Takeda G-protein coupled receptor-5; THR, thyroid hormone receptor; TLR4, Toll-like receptor 4; VLDL, very low-density lipoprotein; VSG, vertical sleeve gastrectomy.

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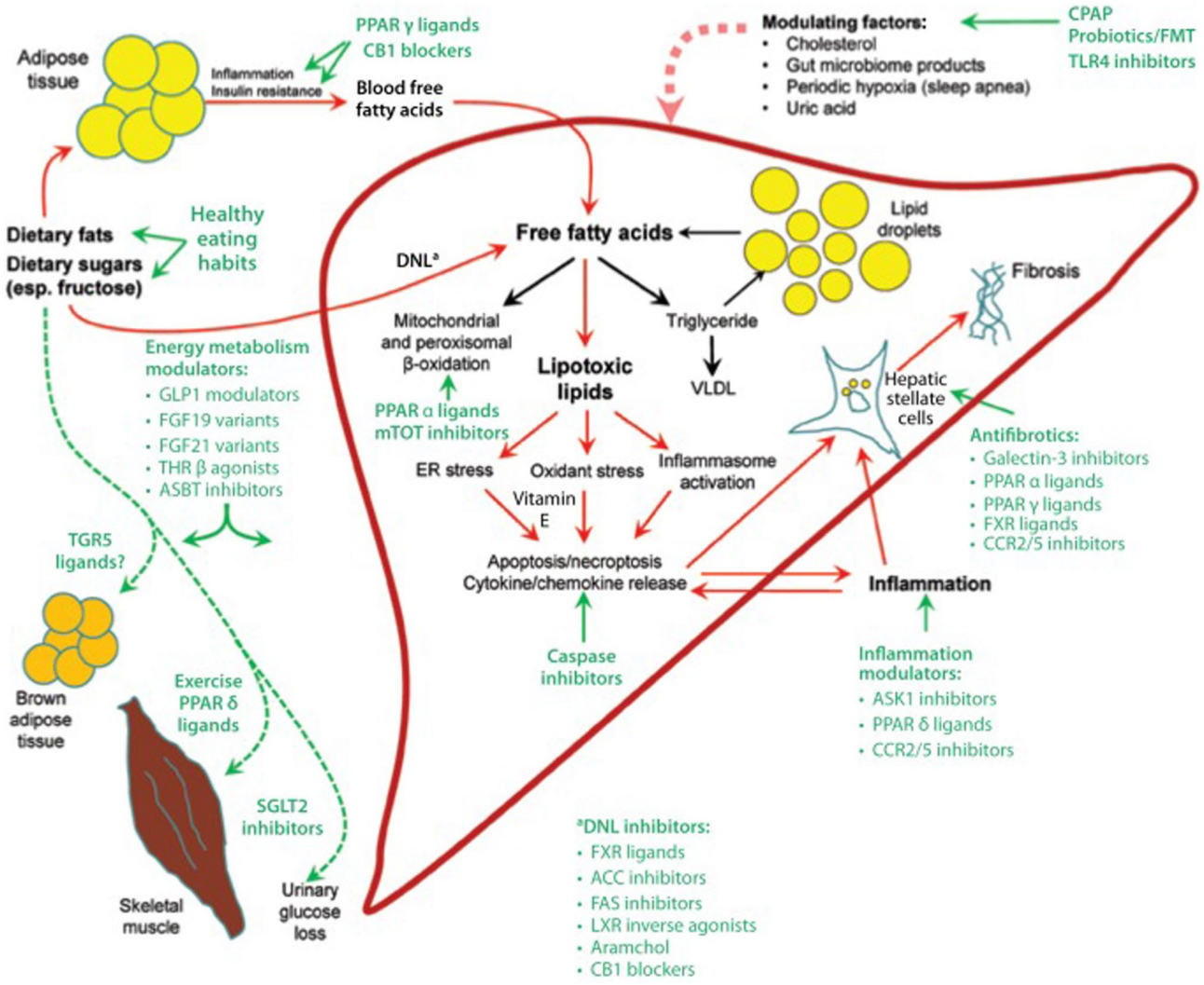

FIG 1 Pathophysiology and pharmacological targets relevant for NAFLD. Reproduced with permission from Gastroenterol Hepatol (N Y.)[13]. Copyright 2018.

NAFLD (Fig. 1) has identified multiple new targets, resulting in numerous phase 1, 2, and 3 studies.[4] Although NASH is associated with increased risk for fibrosis, only fibrosis stage is an independent predictor of liver-related mortality in adults. Therefore, phase 2 or 3 clinical trials predominantly include adults with fibrotic NASH and two primary endpoints: (1) NASH resolution without worsening of fibrosis, and/or (2) fibrosis improvement by ≥1 stage with no worsening of NASH. A few studies target NASH with cirrhosis.

The status of recent multinational phase 3 studies in adults is summarized in Table 1. Obeticholic acid, a farnesoid X receptor (FXR) agonist, had achieved breakthrough therapy designation from the US Food and Drug Administration (FDA), based on promising phase 2 results showing improvement in components of NASH. However, interim 18-month results from the ongoing phase 3 study in adults with definite NASH and fibrosis found both the high dose of 25 mg (23%) and the lower dose of 10 mg (18%) of obeticholic acid achieved the fibrosis endpoint versus placebo (12%), but not the NASH resolution endpoint.[5] To date, even positive clinical trials have achieved the primary endpoint of NASH resolution in only 15% to 50% of patients with NASH, underscoring heterogeneity in NAFLD pathogenesis (Fig. 2). The glucagon-like peptide 1 (GLP1) agonist semaglutide has preliminarily been reported to have achieved 59% NASH resolution versus 17% in placebo in the 0.4 mg once-daily arm of a phase 2 trial of 320 patients over 72 weeks (ClinicalTrials.gov: NCT02970942), but full results are pending.[6] Notably, GLP-1 agonists are currently an already approved treatment for type 2 diabetes in both adults and adolescents and for obesity in adults, and may be a good therapeutic choice for patients with these conditions who have concurrent NASH.

TABLE 1. SUMMARY OF SELECTED MULTINATIONAL PHASE 3 CLINICAL TRIALS IN ADULTS WITH NASH AND FIBROSIS

Active	Target	Trial	Population	Results
Obeticholic acid	FXR analogue	REGENERATE (ClinicalTrials.org: NCT02548351)	NASH, F1-F3 (N = 931)	Interim: superior to PBO in improving fibrosis, 25% versus 12% ($P < 0.01$)
Elafibranor	PPARα/δ ligand	RESOLVE-IT (ClinicalTrials.org: NCT02704403)	NASH, F1-F3 (N = 2000)	Recruiting (primary completion December 2021)
Cenicriviroc	CCR2/5 ligand	AURORA (ClinicalTrials.org: NCT03028740)	NASH, F2-F3 (N = 2000)	Recruiting (primary completion October 2021)
Resmetirom	Thyroid hormone receptor ligand	MAESTRO-NASH (ClinicalTrials.org: NCT03900429)	Suspected/confirmed NASH, F2-F3 (N = 2000)	Recruiting (primary completion June 2021)
Aramchol	Fatty acid bile acid conjugate	ARMOR (ClinicalTrials.org: NCT04104321)	Noncirrhotic NASH, F2-F3, T2DM or prediabetes (N = 2000)	Recruiting (primary completion June 2022)
Selonsertib	ASK1 inhibitor	STELLAR-3 (ClinicalTrials.org: NCT03053050)	NASH, F3 (N = 802)	Terminated: lack of efficacy × 48 weeks
		STELLAR-4 (ClinicalTrials.org: NCT03053063)	NASH compensated cirrhosis (N = 877)	

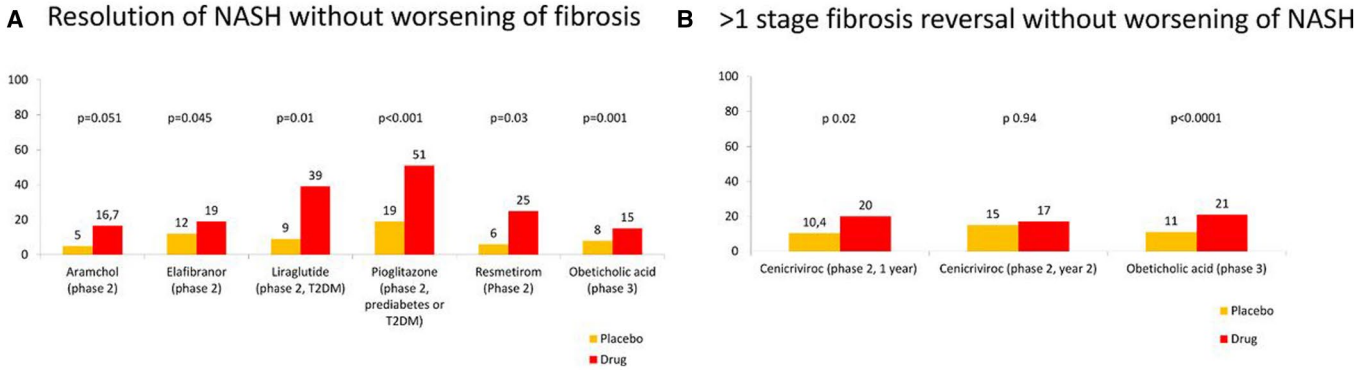

FIG 2 Percentage of patients with (A) resolution of NASH without worsening fibrosis and (B) improvement in fibrosis without worsening NASH in placebo and intervention arms of randomized clinical trials showing an effect. Reproduced from [14]under CC BY-NC 4.0. Copyright 2020.

Although up to 15% of children with NAFLD have advanced fibrosis (F3) at time of diagnosis, only two multicenter randomized, double-blind, placebo-controlled pediatric trials have included histological endpoints: one with three arms (metformin or vitamin E versus placebo) and one with two arms (cysteamine bitartrate versus placebo).[7,8] As in adults, high-dose vitamin E (400 IU twice daily) showed benefit in resolving NASH in children (40% resolution of NASH versus 24% in placebo), but it remains controversial because of unknown long-term safety.[7] Cysteamine bitartrate and metformin were ineffective. The paucity of pediatric studies is in part due to uncertain clinical outcomes of youth-onset NASH, the enhanced need to ensure safety and likely benefit, and the invasive nature of liver biopsy. However, a recent analysis of children receiving standard of care lifestyle advice and placebo showed that although half improved in some histological features of NAFLD, one-third progressed in NASH or fibrosis severity within a 2-year period of follow-up and 5% experienced development of type 2 diabetes.[2] In addition, the rate of young adults with end-stage liver disease is escalating, further highlighting the need to identify effective and safe therapies for youth-onset NASH.

Metabolic bariatric surgery procedures, specifically Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), are well established weight-loss procedures in adults and in adolescents with severe obesity. In addition to yielding significant and sustained mean weight loss of ≈22% to 28%, bariatric surgery consistently yields the highest proportion of patients achieving resolution of NASH (≈80%-85%) in meta-analyses, and even complete resolution of steatosis in one recent meta-analysis (66%; 95% confidence interval [CI]: 56%-75%).[9] Safer than RYGB, VSG has been offered to patients with cirrhotic NASH before, at the time of, and after liver transplantation with good preliminary outcomes.[10] Although adolescent outcome data are scant, pediatric guidelines recommend consideration for surgery in youth with severe obesity and

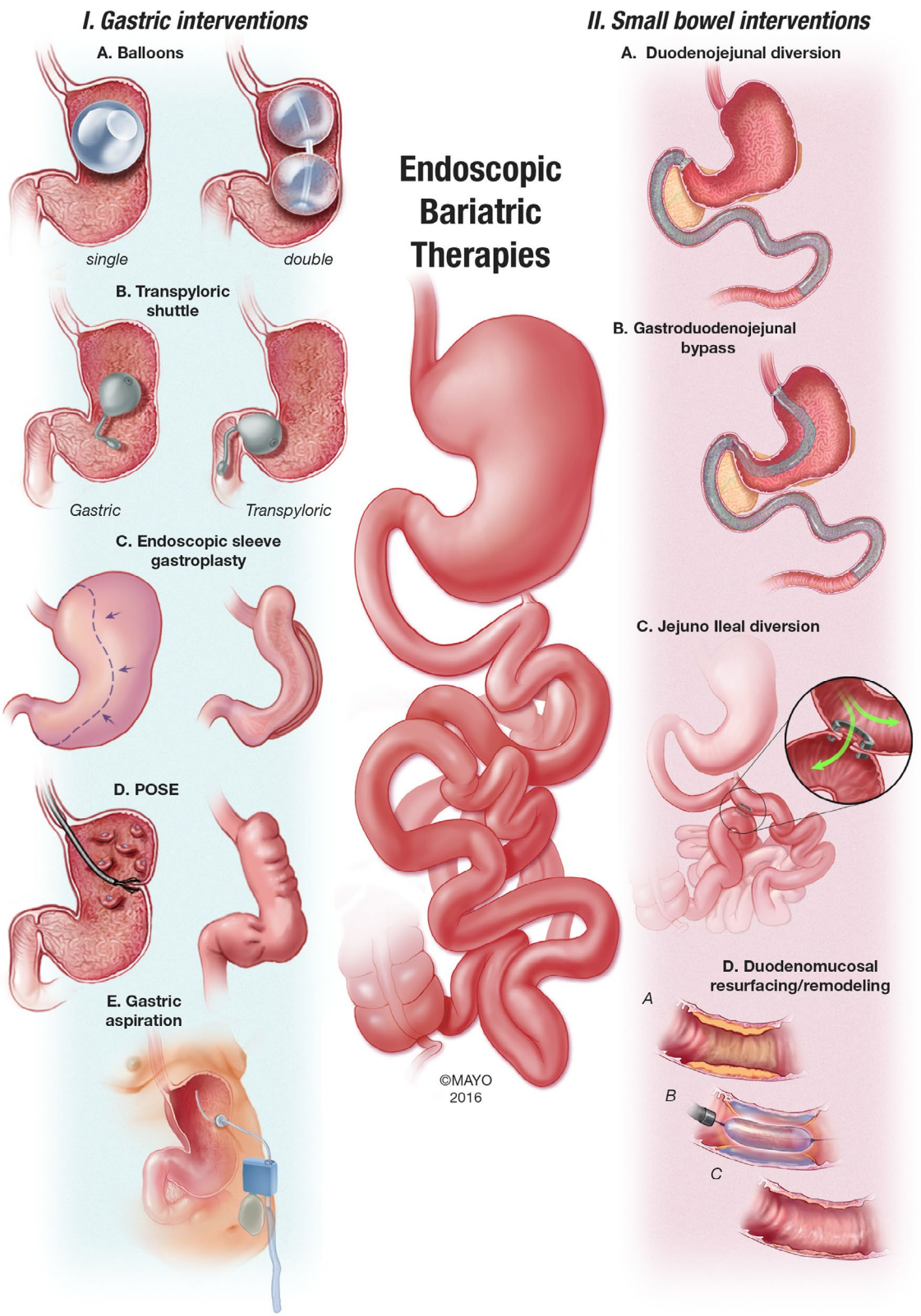

FIG 3 Current types of endoscopic metabolic bariatric procedures. Reproduced with permission from Gastroenterology[15]. Copyright 2017

severe NASH on the basis of the highly positive benefit in adults.[11] In addition to gathering more data in youth, accruing longer-term outcome data in adults is critical, because type 2 diabetes, a condition closely associated with NASH, may recur over time. In addition, bariatric surgery may also result in new or worsening features of NAFLD, including fibrosis in up to 12% of patients (95% CI: 5%-20%).[9]

Although obesity and overweight are strongly associated with NASH, up to 20% of patients have normal body mass index. In addition, not every patient who meets medical criteria is interested in surgery because of potential surgical or nutritional risk. Thus, endoscopic bariatric metabolic procedures (Fig. 3) are rapidly emerging as less invasive and costly therapies for less severe obesity and related complications, including type 2 diabetes.[12] The most studied include a variety of intragastric balloons, endoscopic sleeve gastroplasty, and duodenal mucosal resurfacing. In general, these interventions result in less weight loss than laparoscopic bariatric surgeries (5%-18%), and some are only short term (e.g., intragastric balloons). Observational studies and pilot trials have mainly focused on weight loss, but several have shown improvement in noninvasive markers of NAFLD. More clinical trials are needed to determine optimal candidates and procedures types, the long-term outcomes and safety, and whether there are significant or sustained benefits in histological NAFLD outcomes, compared with lifestyle intervention with or without FDA-approved medications for weight loss (e.g., phentermine-topiramate, naltrexone-bupropion, liraglutide).

In summary, although there are currently no approved medications for NASH, numerous phase 1, 2, and 3 clinical trials are in progress in adults. To date, most clinical trials have achieved resolution of NASH in less than half of patients, highlighting the need for possible combination or more personalized pharmacotherapy. In the interim, high-dose vitamin E or pioglitazone may benefit some adults with confirmed NASH. FDA-approved weight-loss medications may also augment weight loss, together with lifestyle interventions, but have not been studied as specific treatments for NASH. For patients with severe obesity and NASH, laparoscopic metabolic bariatric surgeries (RYGB or VSG) are the most effective treatments currently available, but these are not suitable for nonobese patients with NASH and carry potential surgical and/or nutritional risks. Emerging endoscopic bariatric and metabolic procedures require additional well-designed clinical trials to determine safety and efficacy in patients with NASH. Fortunately, the landscape of pharmacological, endoscopic, and surgical metabolic therapeutic options for NASH is likely to continue to rapidly evolve.

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REFERENCES

1) Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367-378.

2) Xanthakos SA, Lavine JE, Yates KP, et al. Progression of fatty liver disease in children receiving standard of care lifestyle advice. Gastroenterology 2020;23:S0016-5085(20)34996-9. https://doi.org/10.1053/j.gastro.2020.07.034. Online ahead of print.

3) Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.

4) Neuschwander-Tetri BA. Therapeutic landscape for NAFLD in 2020. Gastroenterology 2020;158:1984-1998.

5) Younossi Z, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomized, placebo-controlled phase 3 trial. Lancet 2019;394:2184-2196.

6) NovoNordisk 1st Quarter Earnings Report. Financial report for the period 1 January 2020 to 31 March 2020. Available at: https://www.novonordisk.com/content/dam/Denmark/HQ/investors/irmaterial/quarterly_financial_reports/2020/Financial%20report%20for%20Q1%202020.pdf. Published May 6, 2020.

7) Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305:1659-1668.

8) Schwimmer JB, Lavine JE, Wilson LA, et al. In children with nonalcoholic fatty liver disease, cysteamine bitartrate delayed release improves liver enzymes but does not reduce disease activity scores. Gastroenterology 2016;151:1141-1154.

9) Lee Y, Doumouras AG, Yu J, et al. Complete resolution of nonalcoholic fatty liver disease after bariatric surgery: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:1040-1060.

10) Lee Y, Tian C, Lovrics O, et al. Bariatric surgery before, during, and after liver transplantation: a systematic review and meta-analysis. Surg Obes Relat Dis 2020;16:1336-1347.

11) Armstrong SC, Bolling CF, Michalsky MP, et al. Section on obesity, section on surgery. Pediatrics 2019;144:e20193223.

12) Salomone F, Sharaiha RZ, Boškoski I. Endoscopic bariatric and metabolic therapies for non-alcoholic fatty liver disease: evidence and perspectives. Liver Int 2020;40:1262-1268.

13) Neuschwander-Tetri BA. Pharmacologic management of nonalcoholic steatohepatitis. Gastroenterol Hepatol (N Y) 2018;14: 582-589.

14) Dufour J, Caussy C, Loomba R. Combination therapy for non-alcoholic steatohepatitis: rationale, opportunities and challenges. Gut 2020. https://doi.org/10.1136/gutjnl-2019-319104 (epub ahead of print)

15) Abu Dayyeh BK, Edmundowicz S, Thompson CC. Clinical practice update: expert review on endoscopic bariatric therapies. Gastroenterol Hepatol (NY) 2018;14:582-589.